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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/074,169	02/12/2002	Carl T. Wittwer	7475-70049	5884

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EXAMINER
FREDMAN, JEFFREY NORMAN

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 01/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/074,169	WITTWER, CARL T.	
	Examiner	Art Unit	
	Jeffrey Fredman	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, claims 1-10 in the paper filed December 29, 2003 is acknowledged.

Priority

2. Applicant's claim for priority under 35 U.S.C. 120 is acknowledged. However, the parent application from which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 1-10 of this application. Specifically, there is no support for the final step of claim 1, where "if the call is positive, confirming the positive call by a melting temperature analysis" in the parent application. Therefore, the claims receive a priority date of February 12, 2002.***Double Patenting***

3. Claims 1-10 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-24 of U.S. Patent No. 6,387,621 in view of Herrmann et al (Clin. Chem. (2000) 46(3):425-428).

Claims 1-2 of U.S. Patent No. 6,387,621 teach a method for determining the presence of a nucleic acid comprising the

steps of

(a) providing a fluorescent entity capable of indicating the presence of the nucleic acid and capable of providing a signal related to the quantity of the

nucleic acid,

(b) amplifying the nucleic acid through a plurality of amplification cycles in the presence of the fluorescent entity,

(c) measuring fluorescence intensity of the fluorescent entity at each of the plurality of amplification cycles to produce a fluorescent value for each cycle related to the quantity of the nucleic acid present at each cycle,

(d) generating a fluorescence-verses-amplification-cycle plot wherein the fluorescent values are recorded for each amplification cycle,

(e) calculating slopes of segments of the fluorescence-verses-amplification-cycle plot using a plurality of the

fluorescent values, using the segment slopes of the fluorescence-verses-amplification-cycle plot to establish a baseline fluorescence region by generating a slope value for each of a plurality of the amplification cycles, and establishing the baseline fluorescence region comprising an interval of cycles that includes the amplification cycle with the slope value having an absolute value closest to zero, and ascertaining whether the fluorescence value during a selected amplification

cycle is outside the baseline fluorescence region.

With regard to claim 3, Claims 1-24 of U.S. Patent No. 6,387,621 do not require an internal standard.

With regard to claim 10, Claim 13 of U.S. Patent No. 6,387,621 teaches the automated method.

Claims 1-24 of U.S. Patent No. 6,387,621 do not teach confirmining the results by a melting temperature analysis.

Herrman teaches performing a PCR reaction followed by confirming the target using a melting temperature analysis (see page 425, column 2).

With regard to claim 4, Hermann teaches obtaining a melting profile (see figure 1), determining the minima or miaxima based upon the dF/dT derivative melting curves (see figure 1 and page 427, column 1) and comparing the Tm with the known Tm (see figure 1 and page 427, column 1).

With regard to claims 5-7, Hermann teaches performing the method subsequent to amplification, but MPEP 2144.04 notes "selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results" In this case, with regard to claims 5 and 6, the monitoring step is identical to that performed after amplification and would have been expected to function in the same way during amplification, with the variation simply being an increasing amount of target available to the probe as amplification proceeds, so the order of the steps is prima facie obvious.

With regard to claims 8 and 9, Hermann teaches monitoring fluorescence at 0.1 C/s increments (see page 427, column 1) which encompasses monitoring at longer increments.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the confirmatory melting temperature analysis method of Herrmann with the PCR method of Claims 1-24 of U.S. Patent No. 6,387,621 since Hermann states "The ability to multiplex PCR analysis by color and Tm has many uses in addition to multiplex genotyping. For example, internal amplification controls are often needed for infectious disease and translocation testing to verify that amplifiable DNA or cDNA is present even if the target amplification is negative. Another common need is for multiplexing a competitor as an internal standard for PCR

quantification (see page 428, column 1)." Thus, an ordinary practitioner would have been motivated to confirm the PCR analysis with a melting point analysis in order to perform a variety of checks, including multiplex genotyping, internal controls and internal competitors as standards.

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1 and 4-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ririe et al (Anal. Biochem. (1997) 245:154-160) in view of Passing et al (J. Clin. Chem. Clin. Biochem. (1983) 21:709-720) and further in view of Herrmann et al (Clin. Chem. (2000) 46(3):425-428).

Ririe teaches a method, which uses automated processes such as a fluorometer and computer for plotting, for determining the presence of a nucleic acid (abstract) comprising the steps of: a) providing a fluorescent entity, SYBR Green dye, which is capable of providing a signal indicating the presence and amount of a nucleic acid (page 154, column 2, subheading "Materials and methods"), b) amplifying the nucleic acid through a plurality of amplification cycles in the presence of the fluorescent entity, SYBR green (page 154, column 2, subheading "Materials and methods"), c) measuring the fluorescence of the fluorescent entity during each of the plurality of amplification cycles (page 158, figure 5), d) analyzing the measured fluorescence to determine amplification cyelces for use in establishing a baseline fluorescence region (page 158, figure 5, legend and page 159, figure legend and page 159, column 2 "The integrated melting peak could be used to normalize for instrument or technique variation"), e) ascertaining whether the fluorescent measurement during any of the plurality of amplification cycles is outside the baseline fluorescence region (page 158, figure 5 and page 159, column 2, "Known amounts of control could be added to unknown amounts

of natural template, the templates amplified, melting curves acquired and product melting peaks resolved. The ratio of initial template concentration to internal control concentration would be given by the final ratio of products"). That is, if a baseline control was used to create baseline fluorescent result, the change from this baseline due to the amount of natural template amplified, which would be outside the baseline of the control, would be measured to determine the amount and presence of the natural template nucleic acid.

Ririe does not teach the use of linear regression analysis using the slope of curves and the use of these linear regression data to provide variance measures and to generate well-behaved curves.

Passing teaches the use of linear regression analysis in clinical chemistry methodologies and teaches the analysis to give a regression line based upon a curve with confidence limits into which the method will fall (pages 711-716, see especially figure 1), where significance limits are identified and the methods are compared over multiple cycles or performances (page 714, figure 1).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the method of Ririe with the statistical analysis methods of Passing, since Passing notes in passing that "We now describe a procedure which can achieve all the objectives (i) to (iv) and does not require specific assumptions regarding the distributions of the expected values or the error terms (page 711, column 1)". An ordinary practitioner would have been motivated to apply the well known (at the time of Riries) linear regression methodologies of Passing for use in

comparing control and template melting curves in order to achieve the objectives noted in Passing of testing the null hypotheses, estimating the variables and developing confidence levels to maximize statistical accuracy of the melting temperature comparison. Passing's method was expressly designed for use with clinical chemical methods such as the PCR method of Riries and an ordinary practitioner would have been motivated to use these together for the advantages given above.

Ririe in view of Passing do not teach confirmining the results by a melting temperature analysis.

Herrman teaches performing a PCR reaction followed by confirming the target using a melting temperature analysis (see page 425, column 2).

With regard to claim 4, Hermann teaches obtaining a melting profile (see figure 1), determining the minima or miaxima based upon the dF/dT derivative melting curves (see figure 1 and page 427, column 1) and comparing the Tm with the known Tm (see figure 1 and page 427, column 1).

With regard to claims 5-7, Hermann teaches performing the method subsequent to amplification, but MPEP 2144.04 notes "selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results" In this case, with regard to claims 5 and 6, the monitoring step is identical to that performed after amplification and would have been expected to function in the same way during amplification, with the variation simply being an increasing amount of target available to the probe as amplification proceeds, so the order of the steps is prima facie obvious.

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It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the confirmatory melting temperature analysis method of Herrmann with the PCR method of Ririe in view of Passing since Hermann states "The ability to multiplex PCR analysis by color and Tm has many uses in addition to multiplex genotyping. For example, internal amplification controls are often needed for infectious disease and translocation testing to verify that amplifiable DNA or cDNA is present even if the target amplification is negative. Another common need is for multiplexing a competitor as an internal standard for PCR quantification (see page 428, column 1)." Thus, an ordinary practitioner would have been motivated to confirm the PCR analysis with a melting point analysis in order to perform a variety of checks, including multiplex genotyping, internal controls and internal competitors as standards.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1634